Machine learning versus mechanistic modeling for prediction of metastatic relapse in breast cancer

Sebastien Benzekry

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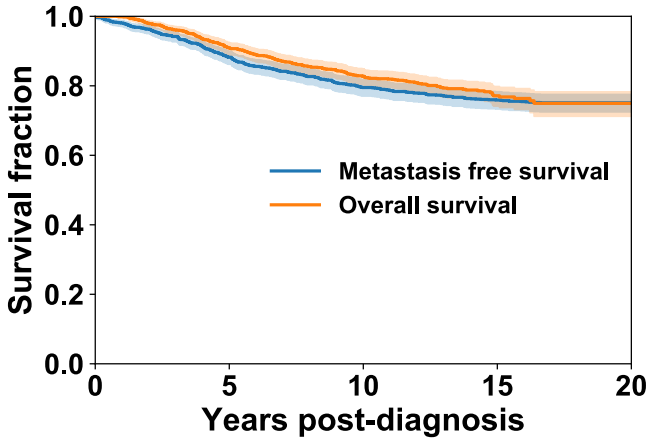
Modeling in ONCology

Breast cancer

- 94% of cases are diagnosed as local or regional but ~30% will relapse
- Estimation of the metastatic risk is key to individualize adjuvant therapy
- Reduce the number of chemo cycles for patients with low risk



Objectives

- Use a mechanistic model to predict metastasis
- Compare to standard survival methods and machine learning algorithms

K = 25 features

n =1057 patients (642 w/o adj)

menopausal_status	ER	PR	Ki67	HER2	HER2_intensity	CK56	EGFR	VIM	ALDH1
Post-ménopause	20	0	0	0	0	0	0	0	0
Ménopause	40	95	8	0	0	0	0	0	0
Activité génitale	87	10	26	0	0	0	0	80	0
Post-ménopause	100	100	8	0	0	0	0	0	0
Post-ménopause	0	0	16	82	+++	0	0	0	0
Activité génitale	100	95	12	0	0	0	0	0	1
Activité génitale	56	100	17	0	0	0	0	0	0
Activité génitale	57	85	23	100	+++	0	0	0	0
Post-ménopause	80	5	20	0	0	0	0	0	0
Post-ménopause	0	0	15	100	+++	0	5	0	0
Post-ménopause	100	80	10	0	0	0	0	0	0
Post-ménopause	30	0	5	0	0	0	0	0	0
Post-ménopause	0	0	15	40	+++	0	0	0	0
Ménopause	0	80	8	0	0	0		0	0
Post-ménopause	0	0	27	0	0	0	30	0	1
Post-ménopause	0	0	56	0	0	80	60	100	0
Activité génitale	50	92	2	1	+	0	0	0	0
Post-ménopause	0	47	5	0	0	0	0	80	0
Post-ménopause	65	0	10	0	0	0	0	60	0
Post-ménopause	100	50	11	0	0	0	0	0	0
Ménopause	20	100	0	0	0	0	0	0	0
Activité génitale	90	6	5	0	0	0	0	0	0
Post-ménopause	100	3	5	0	0	0	0	0	0
Activité génitale	0	0	6	0	0	0	0	0	0
Ménopause	80	100	5	0	0	0	0	0	0
Post-ménopause	100	85	25	0	0	0		0	0
Post-ménopause	10	45	11	13	+++	0	0	0	0
Post-ménopause	66	1	2	40	++	0	0	0	0

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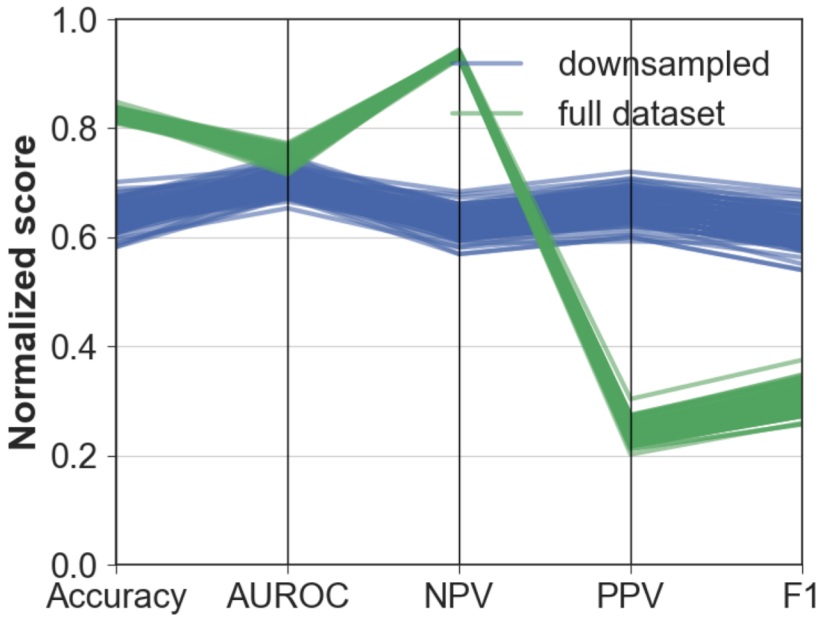
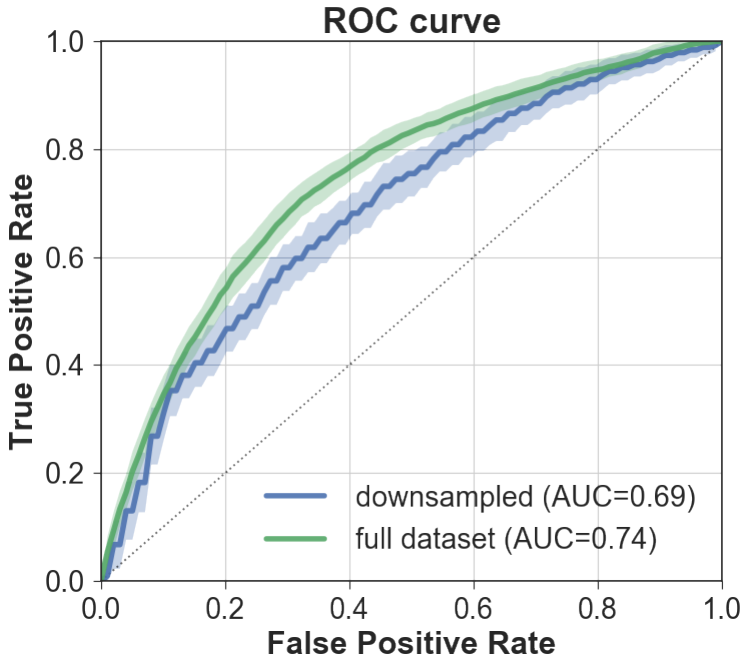
Machine learning for 5-years relapse
Random Forest





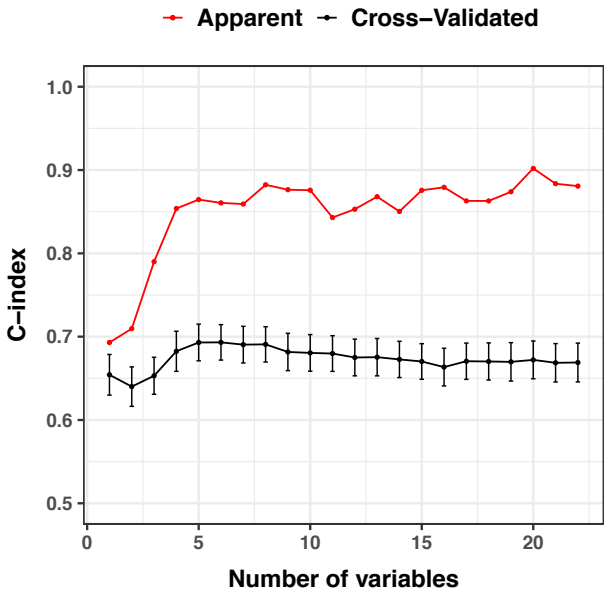
- Classification problem
- Imbalanced data
- Algorithms tested: logistic regression, NN, naïve Bayes, gradient boosting, SVM,…

Does not account for full survival nor censorship ☹

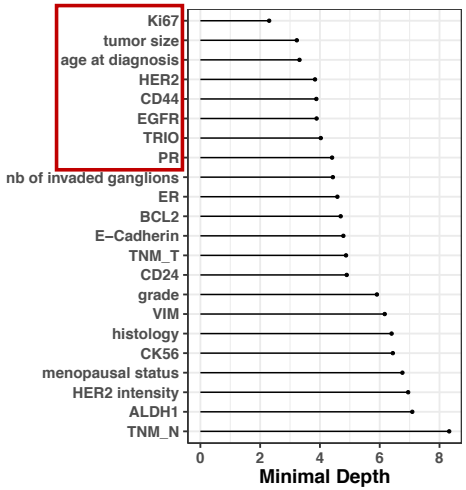
C. Périer

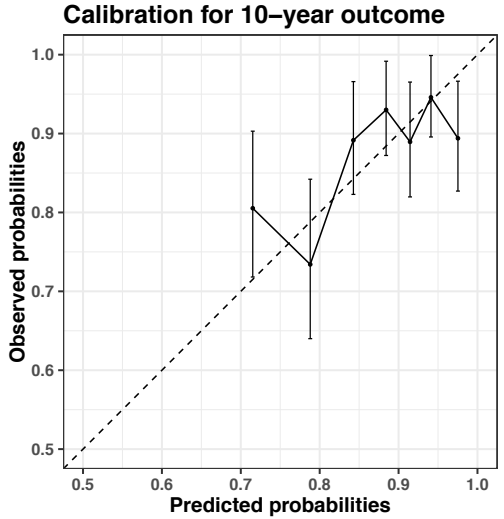
Random survival forests

Accounts for censoring ☺

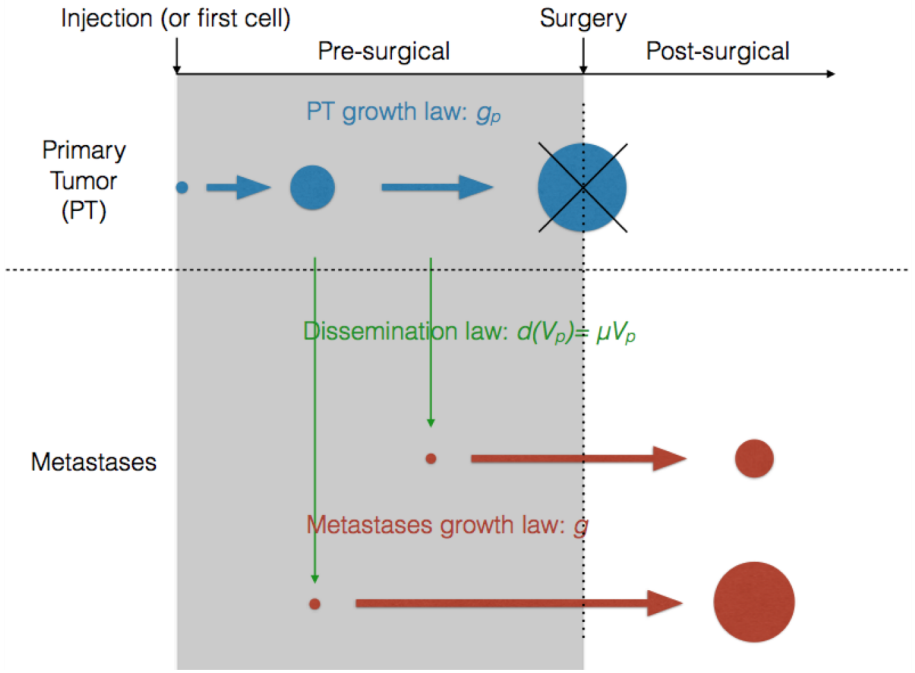


c-index = 0.69





Mechanistic model of metastatic dissemination and growth



Growth rates of primary and secondary tumors g_p and g

$$\frac{dV_p}{dt} = (\alpha_p - \beta_p \ln(V_p))\, V_p \qquad \text{(Gompertz)}$$

$$g(v) = (\alpha - \beta \ln(v))\, v$$

Dissemination rate

$d(V_p) = \mu V_p$

Size distribution of the metastases $\rho(t,v)$

$$\begin{cases} \partial_t \rho(t,v) + \partial_v (g(v)\rho(t,v)) = 0 \\ g(V_0)\rho(t,V_0) = d(V_p(t)) \\ \rho(0,v) = \rho^0 \end{cases}$$

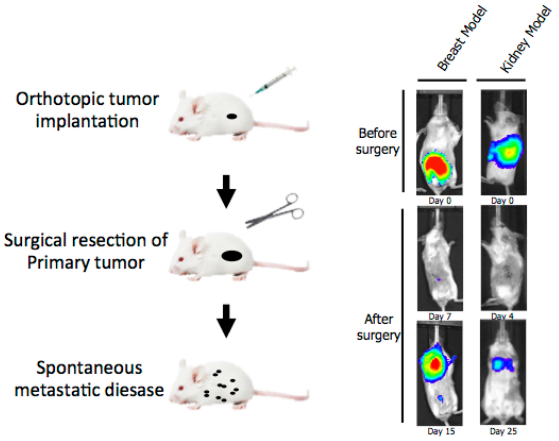
Metastatic burden (total number of metastatic cells)

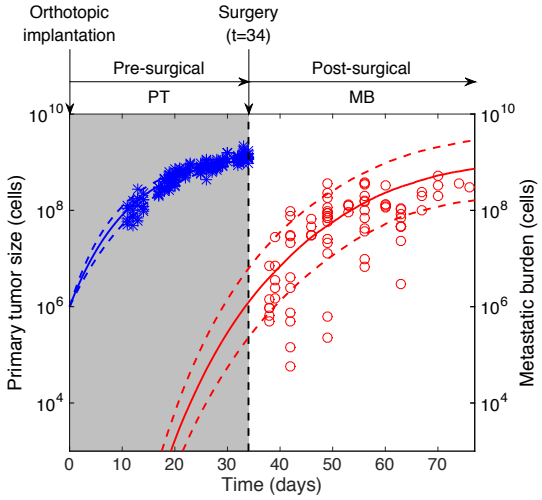
$$M(t) = \int_{V_0}^{+\infty} v\rho(t,v)dv = \int_0^t d\left(V_p(t-s)\right) V(s)ds$$

Iwata et al., J Theor Biol, 2000

Validation on animal data

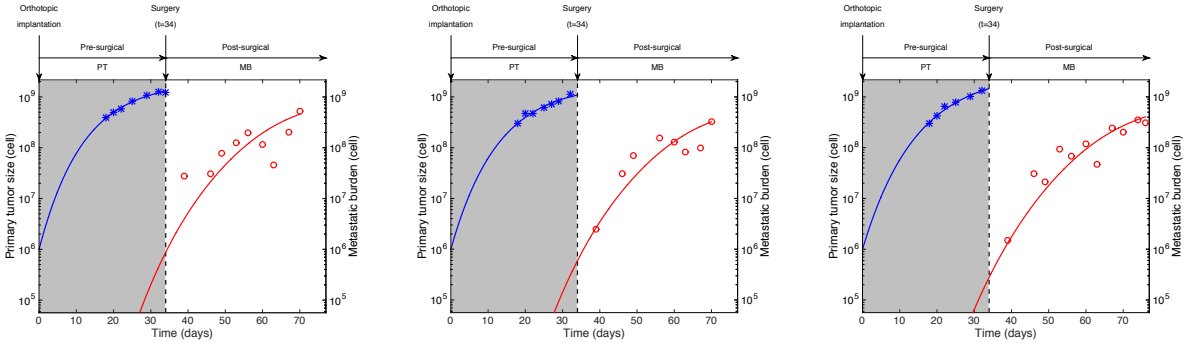
Ebos lab
Roswell Park Cancer Institute





Nonlinear **mixed-effects** statistical model for inter-animal variability

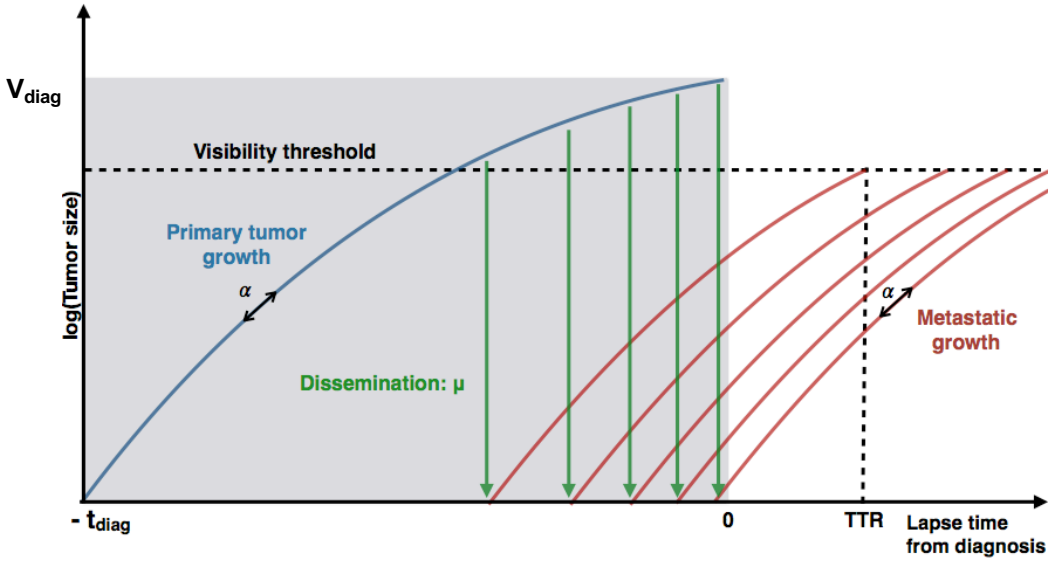
$$\theta^i = \theta_{pop} + \eta_i, \quad \eta_i \sim \mathcal{N}(0, \omega^2)$$



$\Longrightarrow$ **same growth** for PT and mets: $\alpha_p = \alpha$, $\beta_p = \beta$

Benzekry et al. (Ebos), Cancer Res, 2016

Mechanistic modeling of time to relapse



- Number of metastases with size larger than the visible size V_{vis} (= 0.5 cm)

$$N_{vis}(t) = \int_{V_{vis}}^{+\infty} \rho(t, v)dv = \int_{0}^{t-\tau_{vis}} d(V_p(t))dt$$

τ_{vis} = time to reach V_{vis}

- Time to relapse (TTR) defined as the time elapsed from diagnosis to the appearance of a first visible metastasis

$$TTR = \inf\{t > 0 : N_{vis}(t_{diag} + t) \geq 1\}$$

- Parameter β fixed such that $V_\infty = e^{\frac{\alpha}{\beta}} = 10^{12}$ cells

Mixed-effects statistical model

$$\ln\left(T^i\right) = \ln\left(TTR\left(V^i_{diag};\alpha^i,\mu^i\right)\right) + \varepsilon^i, \quad \varepsilon^i \sim \mathcal{N}(0,\sigma^2)$$

(Observation model)

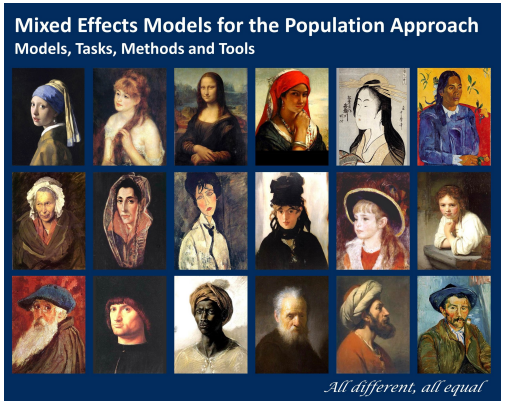
$$S\left(t|\alpha^i,\mu^i\right) = \mathbb{P}\left(T^i > t|\alpha^i,\mu^i\right)$$

Survival function to account for censoring in the likelihood

$$\ln\left(\alpha^i\right) = \ln\left(\alpha_{pop}\right) + \eta^i_\alpha, \quad \eta^i_\alpha \sim \mathcal{N}(0,\omega^2_\alpha)$$
$$\ln\left(\mu^i\right) = \ln\left(\mu_{pop}\right) + \eta^i_\mu, \quad \eta^i_\mu \sim \mathcal{N}(0,\omega^2_\mu)$$

fixed effects

random effects

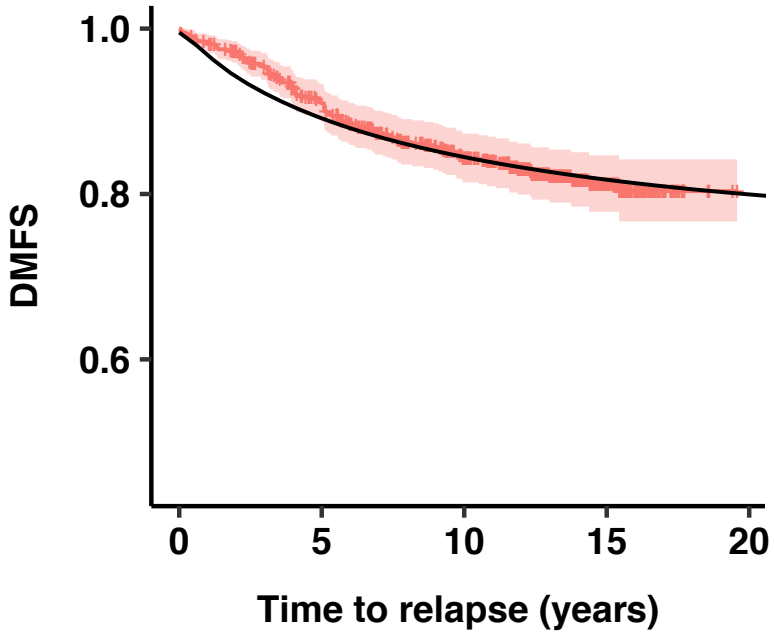


Lavielle, CRC press, 2014

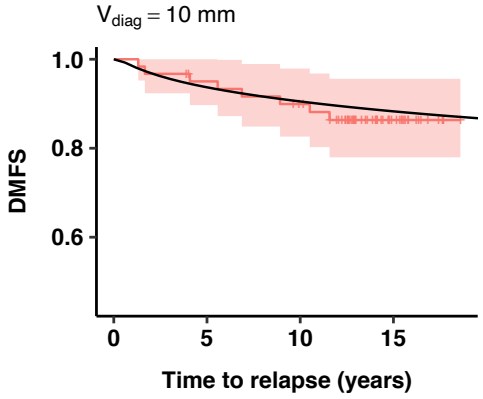
Likelihood maximization performed using the *saemix* R package (SAEM algorithm)

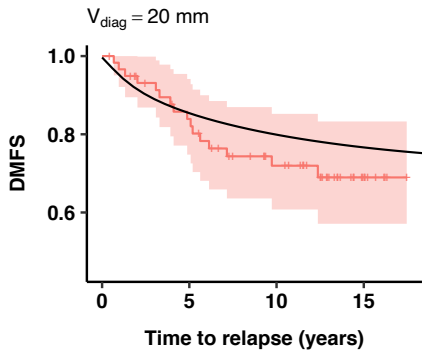
Comets, Lavenu, Lavielle, J Stat Softw, 2017

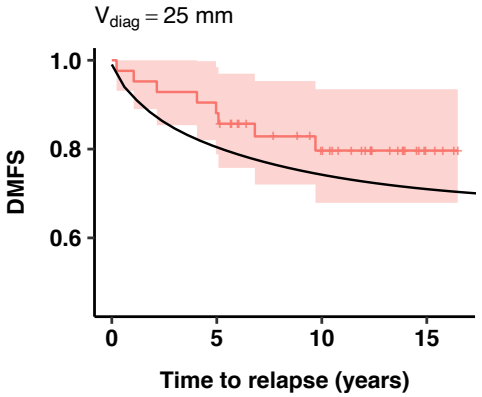
Descriptive power: fit to the data



Parameter	Estimate	r.s.e. (%)
$\log \alpha_{pop}$	-6.337	12.635
$\log \mu_{pop}$	-26.814	3.683
σ	0.542	28.409
ω_α	3.373	36.435
ω_μ	3.780	15.876







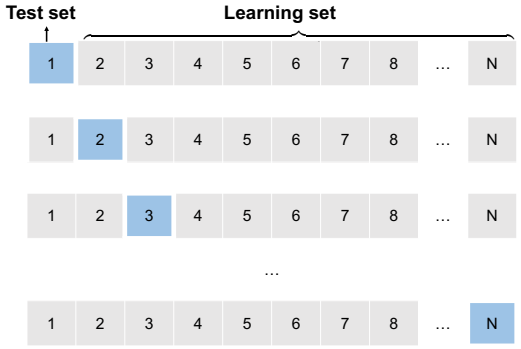
Predictive power: covariates

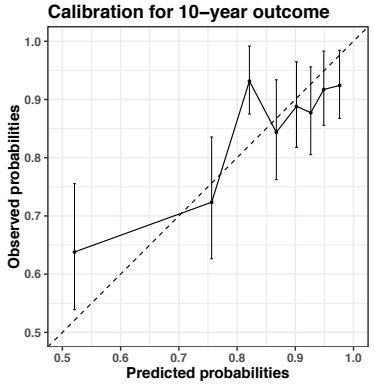
$$\ln\left(\mu^i\right) = \ln\left(\mu_{pop}\right) + \beta_\mu^T \mathbf{x}_\mu^\mathbf{i} + \eta_\mu^i, \quad \eta_\mu^i \sim \mathcal{N}(0, \omega_\mu^2)$$

$$\ln\left(\alpha^i\right) = \ln\left(\alpha_{pop}\right) + \beta_\alpha^T \mathbf{x}_\alpha^\mathbf{i} + \eta_\alpha^i, \quad \eta_\alpha^i \sim \mathcal{N}(0, \omega_\alpha^2)$$

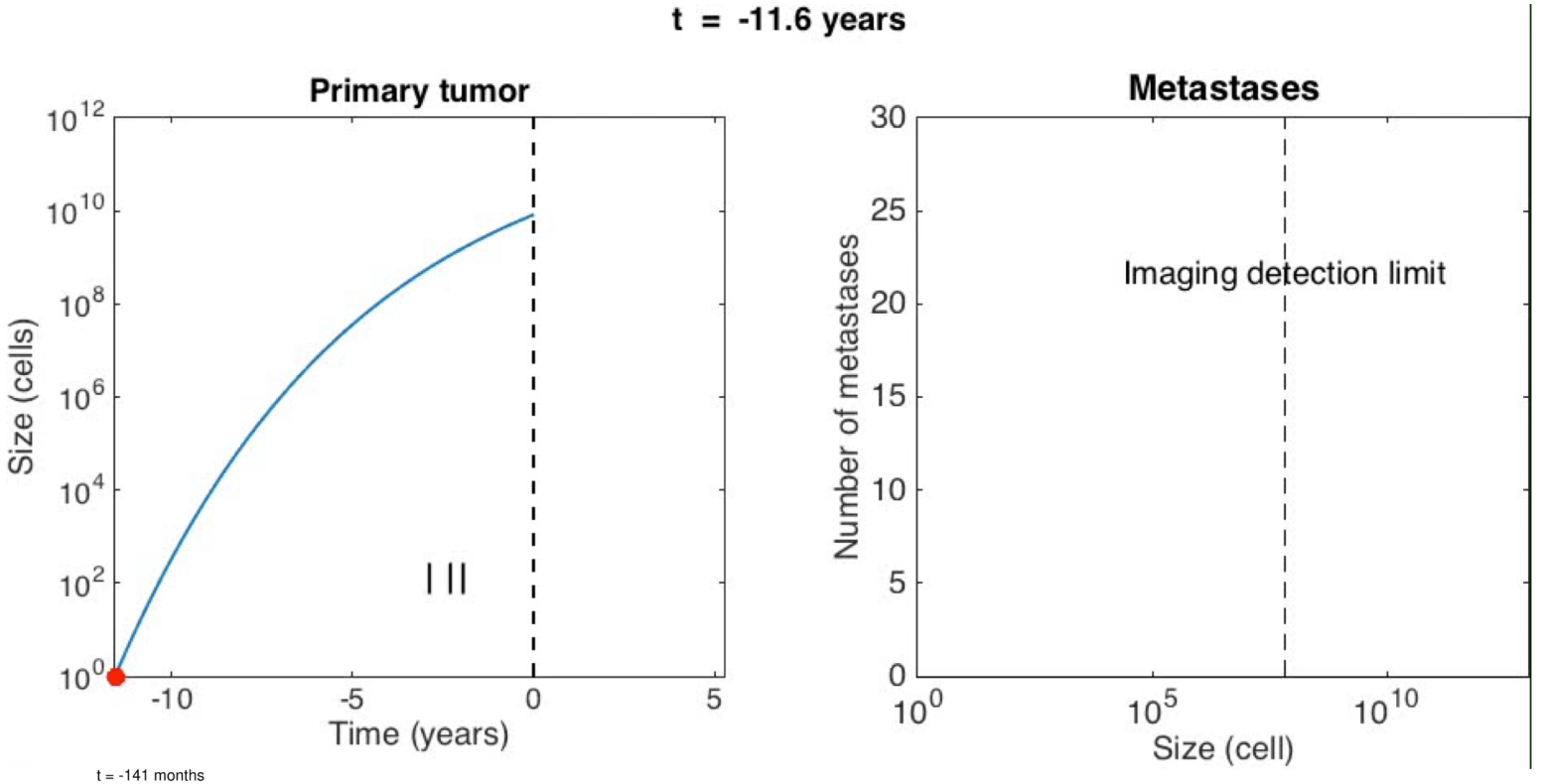
Parameter	Estimate	r.s.e. (%)	p-value
$\log \alpha_{pop}$	-8.883	10.151	
$\beta_{\text{Ki67},\alpha}$	0.086	27.376	$2.59 \cdot 10^{-4}$
$\beta_{\text{HER2},\alpha}$	0.029	42.833	0.020
$\beta_{\text{CD44},\alpha}$	0.011	60.816	0.1
$\beta_{\text{TRIO},\alpha}$	0.016	58.119	0.085
$\log \mu_{pop}$	-26.342	3.696	
$\beta_{\text{EGFR},\mu}$	0.039	47.527	0.035
σ	0.606	23.104	
ω_α	2.062	22.715	
ω_μ	3.563	16.759	

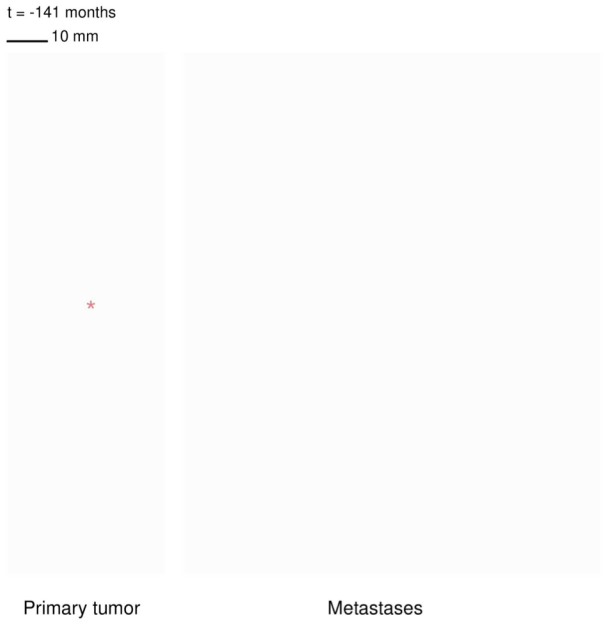
c-index = 0.62 (10-folds cross-validation)

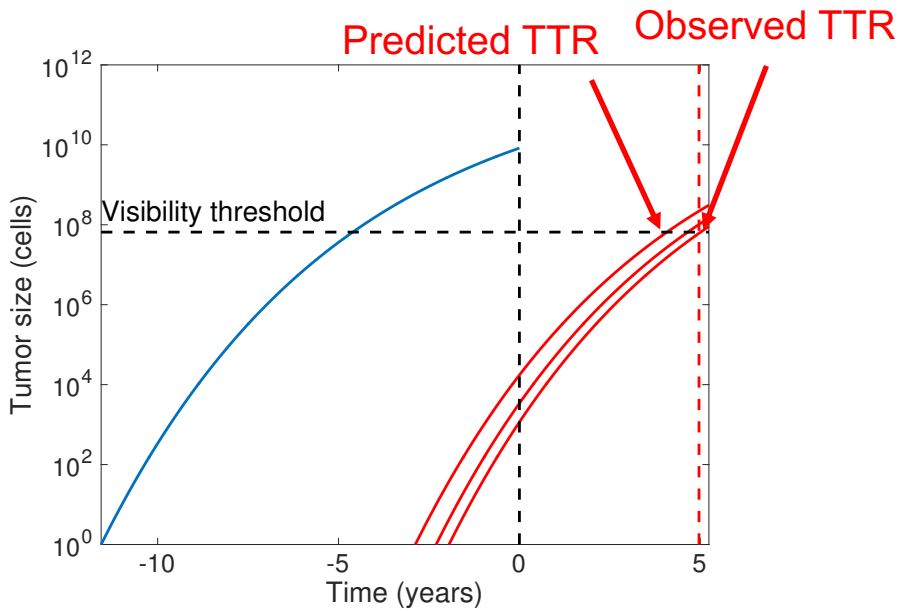


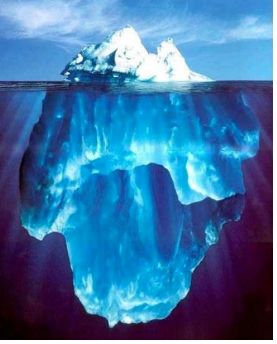


Patient ID	Tumor size (mm)	Ki67	HER2	CD44	TRIO	EGFR	Observed TTR (cens)	Predicted TTR	Prediction error (days)
47	20	32	100	0	0	50	739 (1)	447	292
255	25	1	60	90	60	0	1812 (1)	1609	203
143	18	60	0	50	0	0	2798 (1)	434	2364
12	10	20	0	23	0	0	5970 (0)	$+\infty$	-


t = -11.6 years
Primary tumor
Size (cells)
Time (years)
Metastases
Number of metastases
Imaging detection limit
Size (cell)


t = -141 months
10 mm
Primary tumor
Metastases


Predicted TTR
Observed TTR
Visibility threshold
Tumor size (cells)
Time (years)

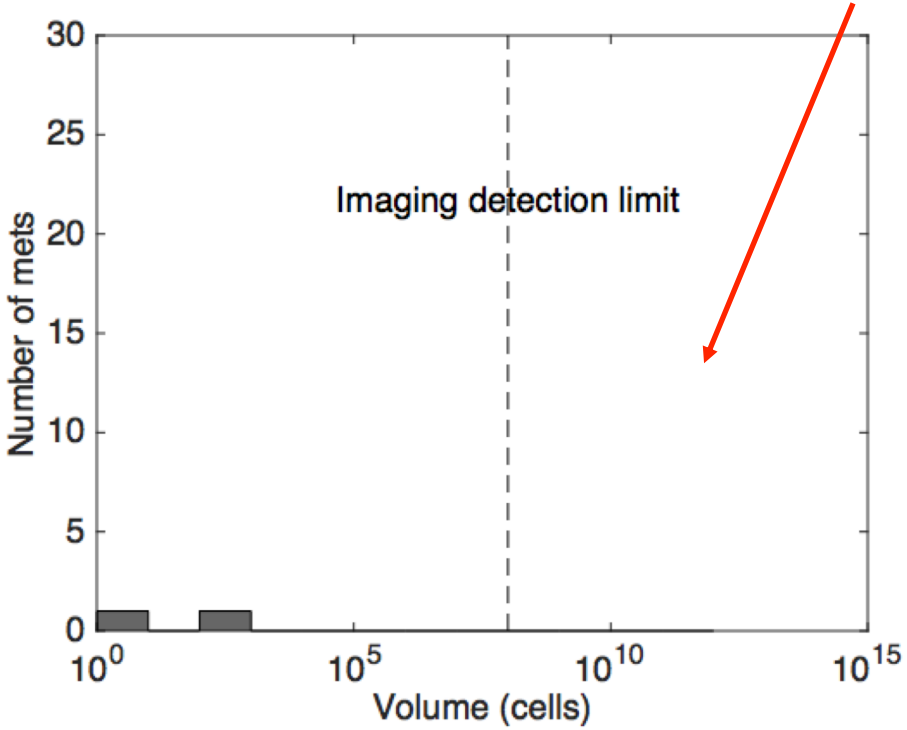


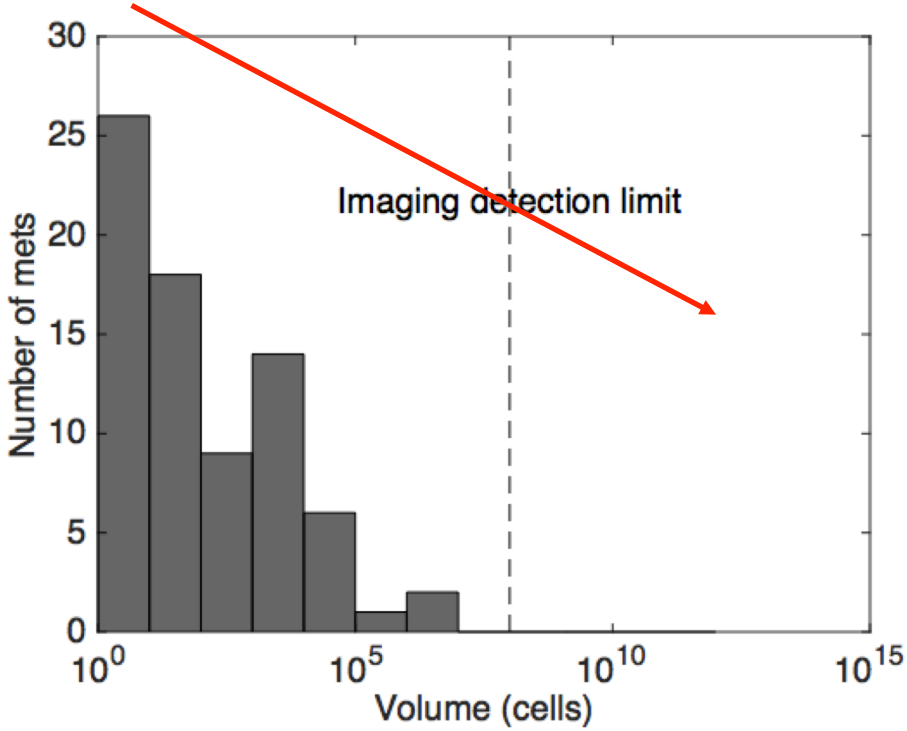
Model-based prediction of metastatic state at diagnosis

Median μ

Large μ (90th prct)

Nothing visible

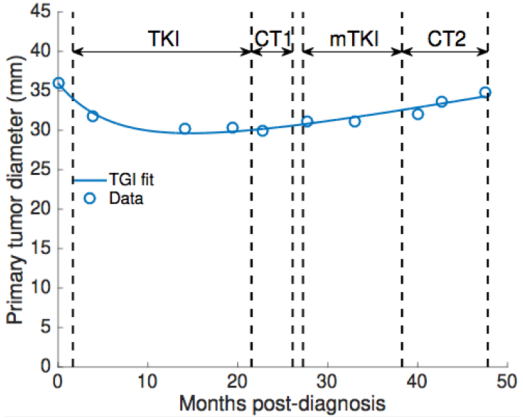




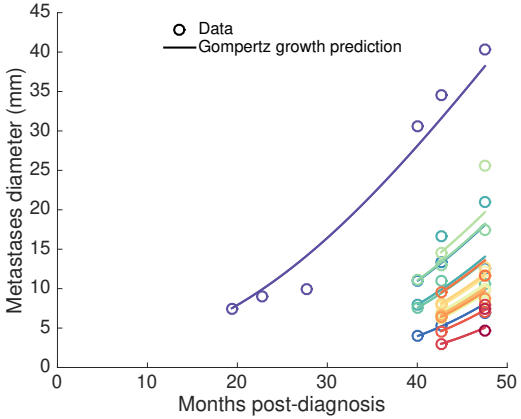
Breast cancer patient with primary tumor of 4.32 cm

Data of a NSCLC patient with brain mets

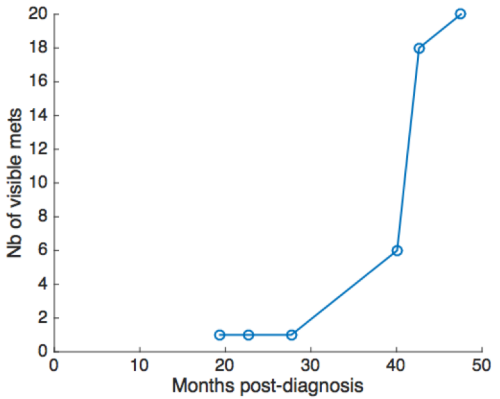
Primary tumor size



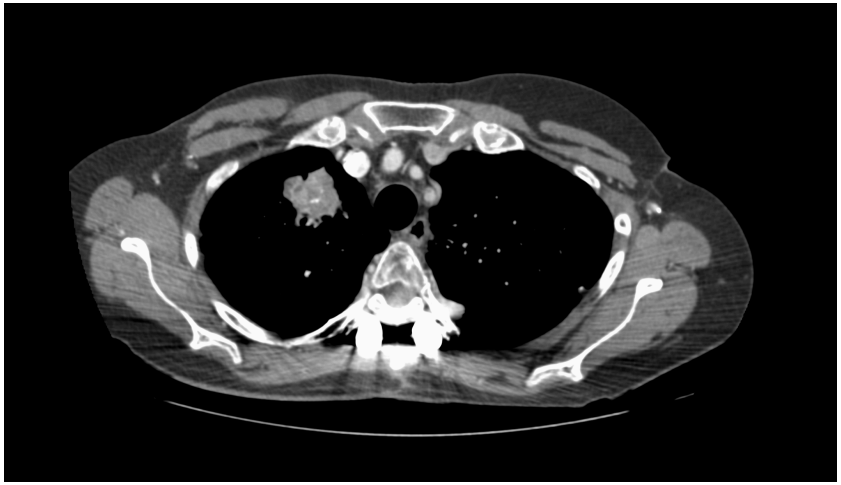
Metastases size



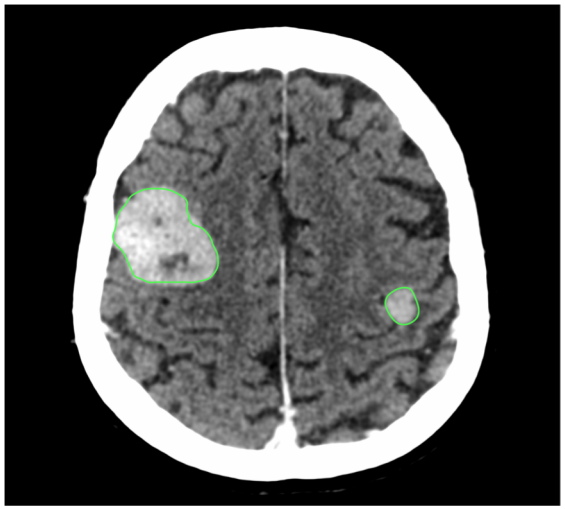
Number of visible mets



Lung CT



Brain CT scan



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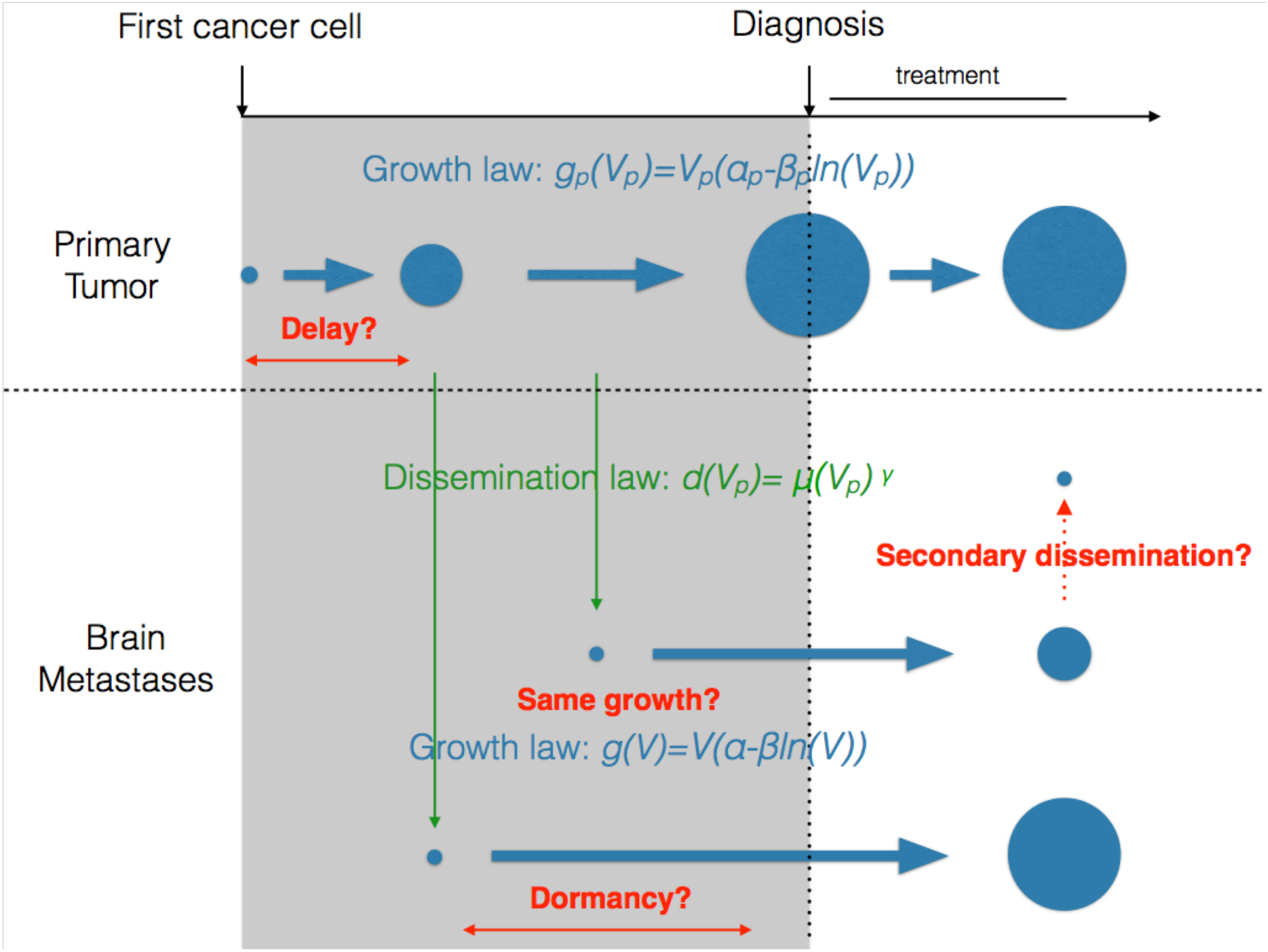
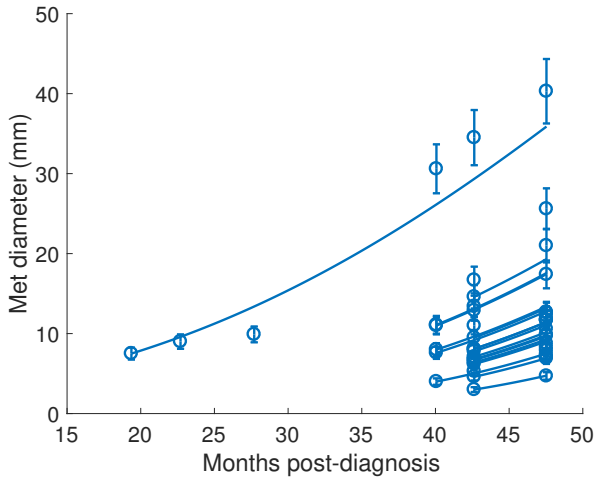
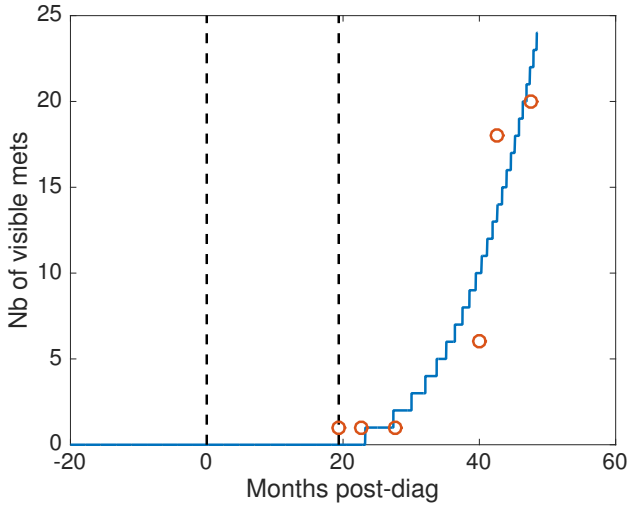

First cancer cell
Diagnosis
treatment
Growth law: $g_p(V_p)=V_p(\alpha_p-\beta_p \ln(V_p))$
Primary Tumor
Delay?
Dissemination law: $d(V_p)= \mu(V_p)^{\gamma}$
Secondary dissemination?
Brain Metastases
Same growth?
Growth law: $g(V)=V(\alpha-\beta \ln(V))$
Dormancy?

The model with dormancy could describe best the data

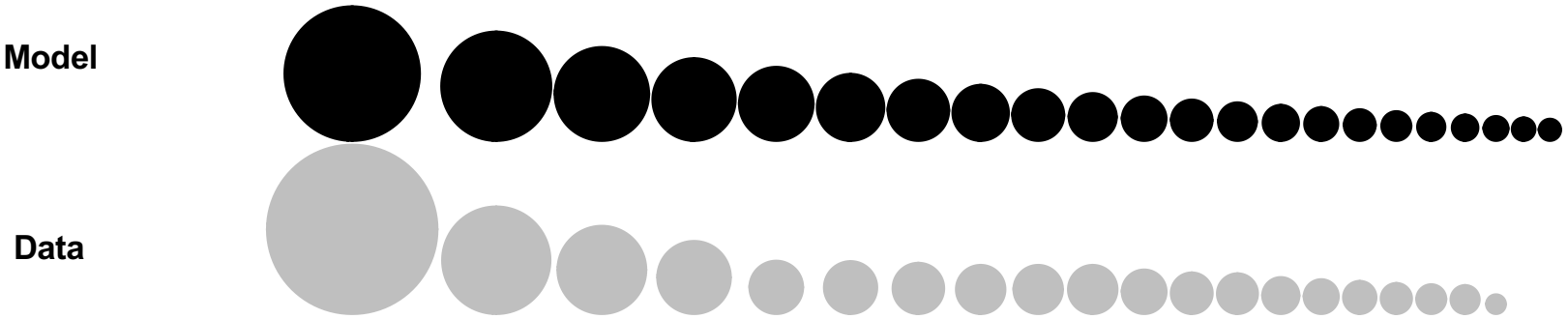




Objective function

Model	Patient 1	Patient 2
Base	5.51	2.53
Secondary	5.43	2.3
Delay	5.23	1.53
Dormancy	4.93	1.71
Diff. growth	4.95	1.79

Dormancy estimated to 133 days ± 4.2%



Bilous et al. (Benzekry), biorXiv, 2018

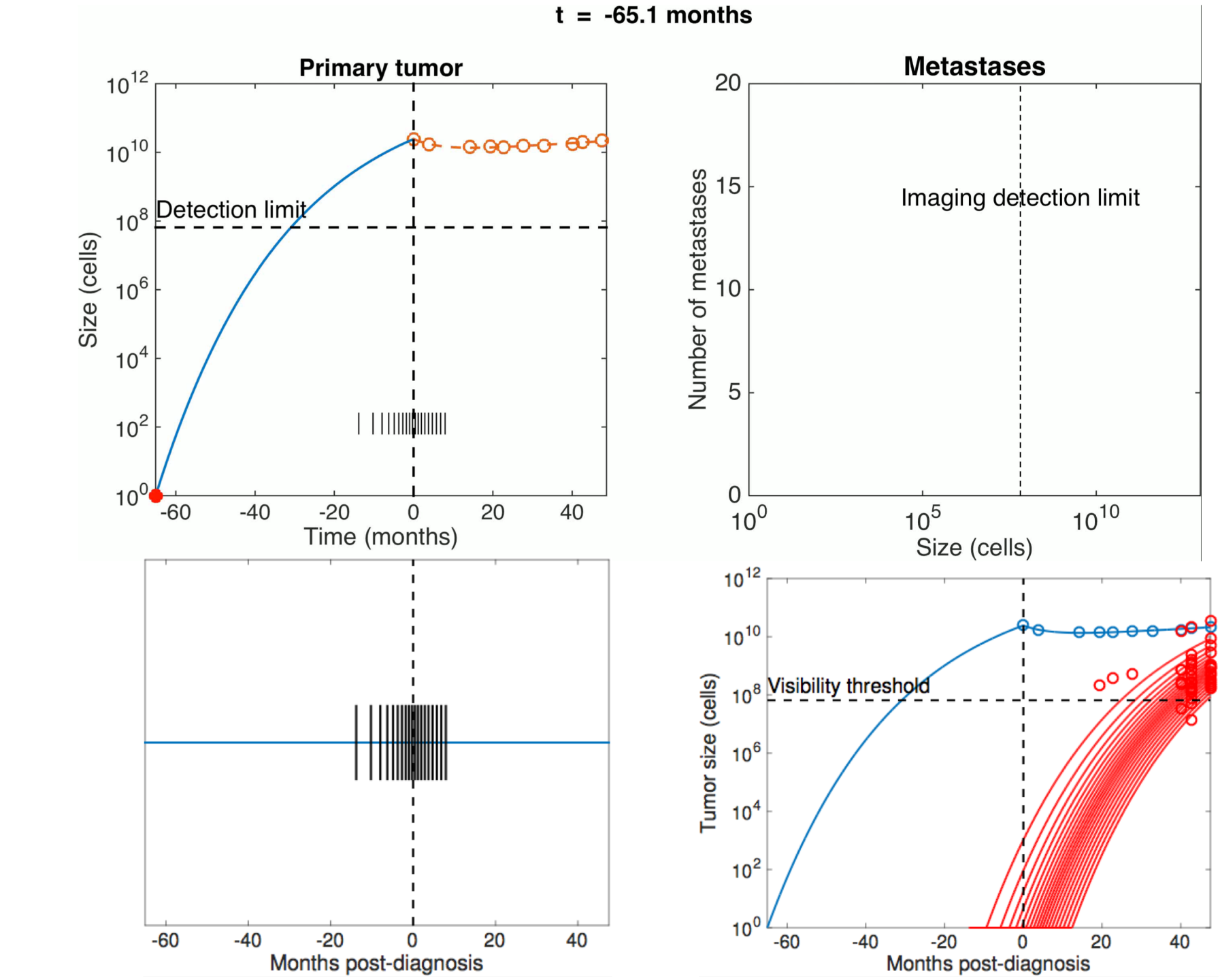
t = -55 months

10 mm

Primary tumor (lung)

Metastases (brain)

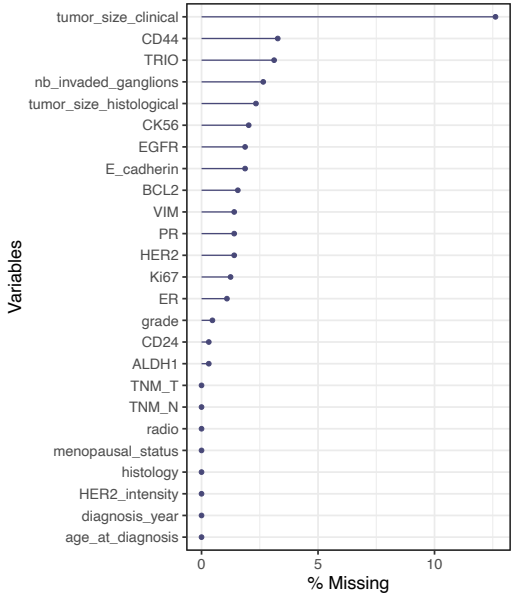
Bilous et al. (Benzekry), biorXiv, 2018


t = -65.1 months
Primary tumor
Size (cells)
Detection limit
Time (months)
Metastases
Number of metastases
Imaging detection limit
Size (cells)
Months post-diagnosis
Tumor size (cells)
Visibility threshold
Months post-diagnosis

Conclusions and perspectives

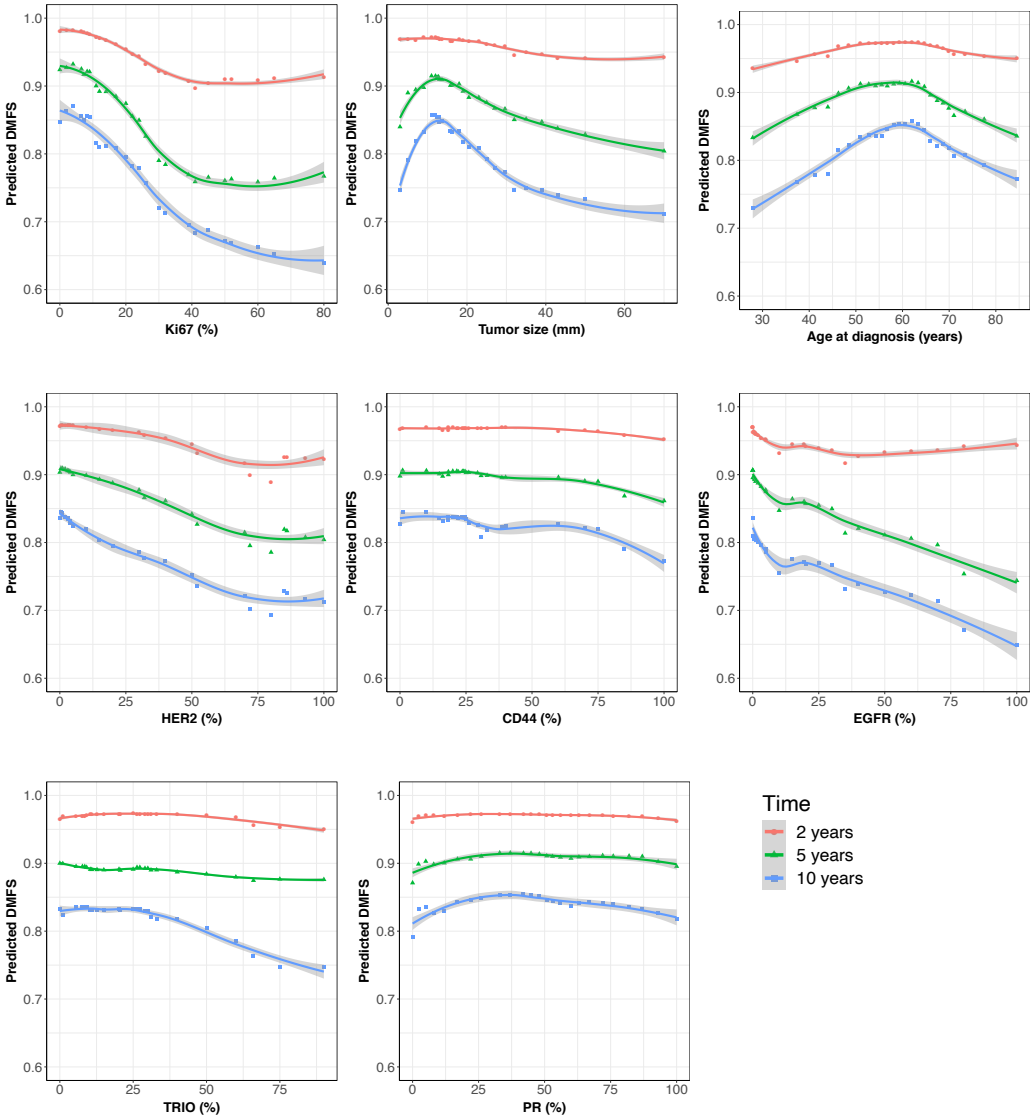
- Machine learning (random survival forest) performed better than the mechanistic model for pure prediction (c-index 0.69 vs 0.62), with similar performances as classical Cox regression (not shown)
- But mechanistic modeling provides biological and clinical insights that ML does not:
  - Ki67 correlates with proliferation rate α (expected but reassurring)
  - HER2 correlates with α, EGFR with μ (metastatic potential)
  - prediction of the **invisible metastatic state** at diagnosis ⇒ potential for **personalized adjuvant therapy**
- This is a first attempt of a mechanistic, individual-level, predictive metastatic model. A lot remains to be done!
  - Refinement to well-established breast cancer molecular subtypes
  - Further investigations to refine the modeling to improve the predictive power
  - Predictive power to be confirmed in external data sets

Supplementary slides



Percentage of missing values in each variable.

Missing covariate values were imputed using an iterative algorithm based on random forests (missForest R package).



Partial dependence plots of the random forest predicted DMFS as a function of the top eight predictors according to the minimal depth ranking.

Results for the Cox regression

	HR	95% CI	p-value
Ki67	1.02	[1.01, 1.03]	$1.71 \cdot 10^{-4}$
Tumor size	1.01	[0.99, 1.03]	0.46
Age	0.99	[0.98, 1.01]	0.49
HER2	1.01	[1.00, 1.01]	0.05
CD44	1.00	[1.00, 1.01]	0.47
EGFR	1.01	[1.00, 1.02]	0.06
TRIO	1.01	[1.00, 1.01]	0.12
PR	1.00	[0.99, 1.00]	0.80

Table S1: Cox regression using the first 8 covariates selected by minimal depth with the random survival forest model.